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FIRST ANNUAL REPORT ON CARCINOGENS

Pursuant to Section 301(b) (4) of the
Public Health Service Act as Amended
by Section 262, PL 95-622

JULY 1980

VOLUME I

Department of Health and Human Services

Prepared by
National Toxicology Program
U.S. Public Health Service

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EXECUTIVE SUMMARY

Department of Health and Human Services

Prepared by
National Toxicology Program
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EXECUTIVE SUMMARY

This First Annual Report on Carcinogens is issued by the Secretary of the Department of Health and Human Services (DHHS) pursuant to Public Law 95-622 which was signed into law on November 8, 1978.* Section 262, Part E, requires that the Secretary of the Department of Health, Education, and Welfare (now DHHS) publish an annual report containing ". . . a list of all substances (i) which either are known to be carcinogens or which may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed. . . ."

Additionally, these annual reports are to provide information on the nature and degree of exposures to such carcinogens and the extent to which Federal regulations are effective in reducing the risk to the public health from exposures to these substances.

This first report discusses a group of 26 chemicals and processes reviewed by panels of international experts and initially found to be associated with the induction of cancer in man.** It also includes information on exposures and on the status of existing regulations of these chemicals.

With this first report, the DHHS begins the long and difficult process of systematically gathering and analyzing significant information about cancer-causing agents in the environment. Further reports will play an important role in informing the public, and those who determine regulatory policy, about the potential human health risks from carcinogens.

Because this is the first report of this type, there are a number of limitations that impeded its full development.

Science and society have not arrived at a final concensus on the definition of carcinogen either in human population or in experimental animals. Scientific judgment plays an important role in the final decision on whether a substance is a carcinogen where test results are unclear. This judgment rests on a knowledge base that is fluid and evolving. However, prudent public health policy dictates that regulation of possibly hazardous substances should not have to wait until there is human evidence of cancer. It is important that evidence from experimental animals be used because society cannot wait until cancer occurs in a population to learn that there is a serious health problem.

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* An amendment to Section 301(b)(4) of the Public Health Service Act.

** See page 3 of the report.

In the past 2 years, progress has been made in defining a carcinogen for regulatory purposes in order to protect the public health. The Interagency Regulatory Liaison Group (IRLG) and the Regulatory Council have issued policy statements endorsing the principle that positive, well-conducted studies on laboratory animals provide strong presumptive evidence of human carcinogenicity. Furthermore, epidemiological evidence--that is statistical studies of human populations--can be used to confirm carcinogenicity in man. These principles have also been incorporated in the Occupational Safety and Health Administration's recently issued cancer policy.

Because of the pioneering nature of this report, only a limited number of carcinogens have been included. The fact that a substance is not included does not mean that it is not a carcinogen. There are more substances than those reported on here which may represent potential health risks to the population. Some of these cancer-causing chemicals are already subject to regulation. The 26 chemicals included represent substances historically viewed as associated with cancer in man. Future reports will deal with chemicals more recently identified as carcinogens, usually through animal studies.

This report will be expanded as the Environmental Protection Agency (EPA) uses its authority under the Toxic Substances Control Act of 1976 (TSCA) to require testing of newly introduced chemicals and of significant new uses of existing chemicals.

The National Toxicology Program will also play a key role in expanding the scope of this report as test results are reported on existing chemicals whose testing has not been required by TSCA.

Estimating the number of people exposed and the nature or route and intensity of exposure remains a difficult problem. Currently, it is difficult, if not impossible, to obtain accurate production and use volumes for most chemicals. In the future, information collected by EPA under TSCA will assist in obtaining this information. But at the moment much of the exposure information is at best an educated guess.

Perhaps the most difficult task is to estimate the effectiveness of Federal regulations in reducing risk. One reason for this difficulty is that virtually all Federal laws concerned with reducing risk to carcinogens have been enacted within the last decade. Thus, given the long period between exposure to a carcinogen and onset of disease, it is difficult to establish the extent to which more stringent regulations of the past decade have reduced risk. Another is that it is particularly difficult to obtain information on past exposure levels to use as a baseline for estimating future risk reduction.

There are two possible ways in which risk reduction might be estimated. The first involves the assumption that risk of cancer is proportional to exposure to the carcinogen. This model assumes extensive information on past and present exposure levels and implicitly assumes that all workplaces are in compliance with the regulations. Information from dose-response studies in laboratory animals can be used to strengthen these estimates; such information has been available only rarely.

Currently, attention is focused on a second way to estimate risk reduction. This method involves applying the results of laboratory animal studies to human health, and discussion focuses on the extent to which such laboratory animal studies are applicable and meaningful in estimating human health risk. As consensus develops, future annual reports will discuss findings in this area.

Categories of Chemicals Catalogued

Lorenzo Tomatis, Director of the Division of Chemical and Biological Carcinogenesis at the International Agency for Research on Cancer (IARC), and colleagues (Cancer Research 38:877, April 1978) divided the chemicals or industrial processes evaluated in the first 16 monographs of IARC into eight major use-exposure categories. In the following discussion, the 26 chemicals and industrial processes fall into five of these categories; namely, naturally occurring substances, industrial chemicals, industrial processes, industrial by-products and pharmaceuticals.

1. Naturally Occurring Chemicals

The aflatoxins are the only chemicals on this list where exposure is principally from natural sources. Other chemicals on this list also exist in nature, to some degree, but their principal source of exposure is elsewhere.

2. Industrial Chemicals

This category of industrial chemicals includes: 4-aminobiphenyl; arsenic; asbestos; auramine; benzene; benzidine; bis(chloromethyl)ether and chloromethyl methyl ether; mustard gas; 2-naphthylamine; soots, tars, and oils; and vinyl chloride. All of these, except auramine, were classified by the 1979 IARC Ad Hoc Working Group as being carcinogenic for humans. Auramine was classified as probably carcinogenic for humans with "lower

degrees of evidence." The 1979 IARC Ad Hoc Working Group then noted that the manufacture of auramine is carcinogenic to humans.

3. Industrial Processes

The industrial processes discussed here include: cadmium and cadmium compounds, chromium and chromium compounds, hematite, and nickel and nickel compounds. All but cadmium and cadmium compounds and hematite were considered by the 1979 IARC Ad Hoc Working Group to be carcinogenic for humans. Cadmium and cadmium compounds were considered to be probably carcinogenic for humans with "higher degrees of evidence." Hematite could not be classified as to its carcinogenicity for humans. However, underground hematite mining was considered to be carcinogenic for humans.

4. Industrial By-Products

The only industrial by-products considered in this report are the isopropyl oils. These oils are formed during the manufacture of isopropyl alcohol. The 1979 IARC Ad Hoc Working Group stated that the isopropyl oil could not be classified as to its carcinogenicity for humans. Manufacture of isopropyl alcohol by the strong acid process was classified as carcinogenic for humans.

5. Pharmaceuticals

This category includes: N,N-bis(2-chloroethyl)-2-naphthylamine, chloramphenicol, cyclophosphamide, diethylstilbestrol (DES), melphalan, oxymetholone, phenacetin, and phenytoin. The 1979 IARC Ad Hoc Working Group classified N,N-bis(2-chloroethyl)-2-naphthylamine, diethylstilbestrol, and melphalan, and as carcinogenic for humans. Cyclophosphamide was classified by the committee as probably carcinogenic for humans with "higher degrees of evidence" while oxymetholone and phenacetin were classified as probably carcinogenic for humans with "lower degrees of evidence." The committee could not classify chloramphenicol and phenytoin with respect to their carcinogenicity for humans due to the inadequacy of the available data.

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Section A provides the context of this report. Section B provides the basis for the selection of the 26 chemicals, and their classification. Section C, the introduction, provides the basis for the pertinent data with respect to each of these chemicals. The Regulatory Council's statement on "Priority Setting for Regulating Chemicals" and the "Mission Statements of Federal Agencies (participating in the report) Having Primary Roles in the Regulation of Chemical Carcinogens" are contained in Section D. The tabular summary of Agency submissions is contained in Section E. Section F contains lists of requests for testing made to the Department of Health and Human Services and their disposition. The appendix is divided into three parts: I. Agency Elaborative Statements on Regulatory Mission; II. Glossary of Abbreviations; and III. List of Participants.

TABLE OF CONTENTS

	Page
A. Foreword	1
B. Introduction	6
C. Categories of Chemicals Catalogued	10
1. Naturally Occurring Chemicals	10
Aflatoxins	11
2. Industrial Chemicals	11
4-Aminobiphenyl	12
Arsenic	12
Asbestos	13
Auramine	14
Benzene	15
Benzidine	16
Bis(Chloromethyl)Ether and Chloromethyl Methyl Ether	17
Mustard Gas	17
2-Naphthylamine	18
Soots, Tars, and Oils	18
Vinyl Chloride	20
3. Industrial Processes	20
Cadmium and Cadmium Compounds	21
Chromium and Chromium Compounds	22
Hematite	23
Nickel and Nickel Compounds	23
4. Industrial By-Products	24
Isopropyl Oils	24

	Page
5. Pharmaceuticals	25
N,N-Bis(2-Chloroethyl)-2-Naphthylamine	25
Chloramphenicol	25
Cyclophosphamide	26
Diethylstilbestrol (DES)	26
Melphalan	27
Oxymetholone	27
Phenacetin	28
Phenytoin	29
D. The Regulatory Council's Statement on Priority Setting for Regulating Carcinogens and on Carcinogen Related Missions of NTP Participating Agencies	29
1. Setting Priorities for Regulating Chemicals	30
2. The Carcinogen Related Missions for NTP Participating Agencies	32
E. Summary of Agency Submissions	36
F. Requests to DHHS for Testing Chemicals and Their Disposition--and to Provide Information	71
Appendices	
I. Agency Elaborative Statements on Regulatory Mission	124
II. Glossary	142
III. Participants	149

FIRST ANNUAL REPORT ON CARCINOGENS

A. Foreword

Cancer, the Nation's number two killer, will take the lives of almost 400,000 Americans this year. Cancer is associated with great financial loss as well as suffering to individuals and their families. Rough estimates of its total direct and indirect costs to the Nation, including medical costs and lost productivity, range up to $30 billion a year.

Americans have become increasingly concerned about the risk of environmental and occupational cancer. As one by one new chemical agents in our air, water, and food, and other factors such as smoking, have been identified as possible cancer-causing agents, the public has turned toward the government for answers. Clearly the public wants to know which of these agents in the workplace and in the general environment are serious hazards, and how well the government is protecting the public health by controlling these agents.

The systematic identification of chemical carcinogens by the government began, not as a regulatory tool, but rather as a research effort conducted primarily by the Carcinogenesis Testing Program at the National Cancer Institute, National Institutes of Health, of the Department of Health, Education, and Welfare, now the Department of Health and Human Services. Accordingly, priorities for testing were determined more often by research interests than by particular regulatory needs.

With this First Annual Report on Carcinogens, the Department of Health and Human Services (DHHS) begins the long and difficult process of systematically gathering and analyzing significant information about cancer-causing agents in the environment. Further reports will be issued annually and will play an important role in informing and educating the public, and those who determine regulatory policy, about the potential human health risks from carcinogens.

Although various Federal Agencies have been collecting information on and regulating carcinogens for several years, this is the first time that an attempt has been made to bring these data together in one report as intended by Congress. Thus, because of its pioneering nature, this first report is necessarily limited in scope to only a limited number of carcinogens. The fact that a substance is not included in this first annual report does not mean that it is not a carcinogen. There are more substances than those included which may represent potential health risks to the population.

Critical to a judgment of the risk posed by a particular carcinogen is an understanding of how people can be exposed to it. As this first report is written, exposure data are imperfect. However, as subsequent annual reports are issued, this list, its exposure data and risk assessments, will become more sophisticated.

Science and society have not arrived at a final consensus on the definition of a carcinogen either in human populations or in the experimental animals which are used to test for cancer-causing potential in man. However, in the past 2 years, progress has been made in defining these questions for regulatory purposes to protect the public health. Two United States government reports have dealt with this important issue: the Interagency Regulatory Liaison Group's (IRLG) risk assessment document[1] and the Regulatory Council's carcinogen policy.[2] Both of these reports support the principle that positive, well-conducted studies on laboratory animals provide strong evidence that a substance may be presumed to be a human carcinogen and that epidemiological evidence--that is, statistical studies made of human populations--can be used to confirm the carcinogenicity of substances in man. The Occupational Safety and Health Administration (OSHA) adopted the same principles in its generic cancer policy.[3] Moreover, the International Agency for Research on Cancer (IARC), part of the World Health Organization, has spelled out its definitions in a recent document, IARC Supplement 1, 1979.

Although scientific judgment in the area of carcinogenesis is fluid and evolving, these definitions will influence the inclusion of chemicals in this and future reports. In response to growing

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1 The IRLG, established to coordinate Federal policy toward health hazards, consists of the Consumer Product Safety Commission (CPSC), the Department of Agriculture's Food Safety and Quality Service (FSQS), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and OSHA. The document is entitled "Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks", was published in the Federal Register on July 6, 1979.

2 The Regulatory Council is a group of 18 executive and 18 independent agencies which monitors and coordinates regulatory activity. Its "Statement on Regulation of Chemical Carcinogens" was published in the Federal Register on October 17, 1979 (see page 60038-60041).

3 "Identification, Classification and Regulation of Potential Carcinogens" was published in the Federal Register, January 22, 1980.

scientific knowledge of their possible hazard, as several Federal Agencies are developing policies to limit exposure to carcinogens, this annual report becomes an important tool in public health protection.

The language of the statute calling for this report requires the inclusion of ". . . all substances which either are known to be carcinogens or . . . may reasonably be anticipated to be carcinogens. . . ." The legislation does not require scientific proof of carcinogenicity for a substance to be included on the list.

Twenty-six compounds, most of which were identified through scientific consensus many years ago, have been included in this first report. The data on these chemicals have been peer reviewed and published in the first of the 16 IARC monographs. Thus, the regulatory and scientific communities were given sufficient lead time so that when appropriate legislation was enacted, they could respond--the regulators with regulatory strategies and the scientific community with strong scientific consensus.

Many of the 26 compounds also were first associated with cancer in human populations. Prudent public health policy, as is demonstrated by recent trends in regulatory legislation, is designed to prevent human exposure to hazardous substances. We do not want to wait until human disease occurs before we learn there may be a problem. But the realization that properly conducted laboratory animal studies do predict which chemicals can cause cancer in human populations has evolved only in the last decade.

It is important to note that the chemicals discussed in detail in this report do not represent the total of all substances confirmed or suspected to be potential carcinogens. The National Institute for Occupational Safety and Health (NIOSH) has published a list of 34,000 toxic substances, 2,330 of which have one or more unevaluated studies dealing with tumorigenicity.[4] The participating regulatory agencies have already regulated additional chemicals on the basis of their carcinogenicity not included in the 26 chemicals discussed herein; OSHA is preparing a list of candidate substances requiring further analyses before moving to regulation. Thus, this report must be viewed as one part of the total public and private effort to identify and control chemical carcinogens. These 26 chemicals represent those substances that have been historically viewed as associated with cancer in man. Future annual reports will deal primarily with chemicals more recently identified as carcinogens, usually through animal studies.

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4 "Registry of Toxic Effects of Chemical Substances", NIOSH, 1978. Approximately a third of these 2,330 substances are possible carcinogens.

While from the standpoint of public health protection, it is extremely important that regulatory definitions of carcinogens such as those of the IRLG, OSHA, and the Regulatory Council are being established; scientific judgment will continue to play an important role in analyzing the results of animal studies.

These annual reports will be broadened to include new substances as the EPA its authority under the Toxic Substances Control Act of 1976 (TSCA) to require safety testing on newly developed chemicals and on significant new uses of existing chemicals. Data from TSCA studies will be incorporated into future reports.

The National Toxicology Program (NTP)[5] will also play a key role in increasing the scope of these annual reports by testing existing chemicals. NTP is also active in developing new, less expensive and quicker test methods than the standard animal bioassay. When perfected, these methods will help test even more chemicals.

Estimating Exposure

Estimation of exposure--which involves estimating the number of people exposed and the nature or route and intensity of exposure--is another difficult problem. Currently, it is difficult, if not impossible, to obtain accurate production and use volumes for most chemicals. In future years, the information collected by the EPA under TSCA will assist in obtaining this information.

Data regarding exposure levels in occupational and envionmental settings are certainly not as complete as we would like. This Department's National Occupational Hazard Survey (NOHS), conducted from 1972 to 1974, gave good information on the number of workers exposed, as well as the first information, in a qualitative sense, on the broader aspects of occupational exposure levels. The forthcoming NOHS II should yield important new information with respect to more recent exposure. Subsequent annual reports on carcinogens will explore other available data bases and their strengths and limitations. But at the moment much of the exposure information is at best an educated guess.

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5 NTP's Executive Committee includes FDA, OSHA, CPSC, EPA, NIOSH, the National Cancer Institute (NCI), and the National Institute of Environmental Health Sciences (NIEHS).

Reducing Risk

Perhaps the most difficult task is to estimate the effectiveness of Federal regulations in reducing risk. One reason for this difficulty is that virtually all Federal laws concerned with reducing risk to carcinogens have been enacted within the last decade. Thus, given the long period between exposure to a carcinogen and onset of disease, it is difficult to establish the extent to which more stringent regulations of the past decade have reduced risk. Another is that it is particularly difficult to obtain information on past exposure levels to use as a baseline for estimating future risk reduction.

The regulation of asbestos in the workplace provides a good example of the problem. In 1969 under the Walsh-Healy Act, which regulates only firms with government contracts, the standard for permissible exposure was 12 fibers of asbestos per cubic centimeter (cc). Under the OSHA Act, this standard was reduced to 5 fibers/cc in 1972 and 2 fibers/cc in 1976. On April 17, 1980, a joint NIOSH-OSHA Working Group recommended that all non-essential uses of asbestos be eliminated and that a public health program to reduce human exposures be implemented. The extremely high risk to workers heavily exposed prior to 1969 is well known, but data on exposure levels in the forties, fifties, and sixties are fragmentary. Mesothelioma (primarily an asbestos-induced cancer) and lung and other cancers, whose incidence is increased by asbestos exposure, generally take 20-40 or more years to develop and become apparent. Therefore, we will not know until early in the next century the extent to which the series of exposure reductions in seventies have reduced the cancer risk of those exposed to asbestos.

There are two possible ways in which risk reduction might be estimated. The first involves the assumption that risk of cancer is proportional to exposure to the carcinogen. This model assumes extensive information on past and present exposure levels and implicitly assumes that all workplaces are in compliance with the regulations. Information from dose-response studies in laboratory animals can be used to strengthen these estimates; such information has been available only rarely.

Currently, attention is focused on a second way to estimate risk reduction. This method involves applying the results of laboratory animal studies to human health, and discussion focuses on the extent to which such laboratory animal studies are applicable and meaningful in estimating human health risk. As consensus develops, future annual reports will discuss findings in this area.

B. Introduction

The Community Mental Health Centers Act, Amendments, Section 262, PL 95-622, Part E, signed November 8, 1978, establishes a requirement that the Secretary of the Department of Health, Education and Welfare (DHEW) (now the Department of Health and Human Services (DHHS)) publish an annual report which contains:

> "(A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;
>
> "(B) information concerning the nature of such exposure and the estimated number of persons exposed to such substances;
>
> "(C) a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency; and (ii) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance; and
>
> "(D) a description of (i) each request received during the year involved--
>
> > "(I) from a Federal agency outside the Department of Health, Education and Welfare for the Secretary, or
> >
> > "(II) from an entity within the Department of Health, Education and Welfare to any other entity within the Department
>
> to conduct research into, or testing for, the carcinogenicity of substances to provide information described in (ii) of subparagraph (C), and (ii) how the Secretary and each such other entity, respectively, have responded to each request."

The National Toxicology Program (NTP) was delegated the responsibility within DHHS for implementation of this Section. The intent of this legislation and the first annual report is to better focus and coordinate the Federal agencies' efforts to protect the public health from carcinogenic agents, to provide information that will be useful to regulatory agencies in increasing the degree of public

health protection, and to provide a source of information for the public and policy makers in both the private and public sectors. Agencies participating in this effort include:

Center for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH)

Consumer Product Safety Commission (CPSC)

Environmental Protection Agency (EPA)

Food and Drug Administration (FDA)

National Institutes of Health/National Cancer Institute (NIH/NCI)

National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS)

Occupational Safety and Health Administration (OSHA)

A key issue in the development of this first report was arriving at a consensus definition of the term carcinogen. In the interest of expeditiously initiating issuance of the first report, the decision was made to proceed with the list of chemical carcinogens described in the IARC monographs (Volumes I through XVI), Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man.

In 1971, IARC, a World Health Organization agency based in Lyon, France, began a program to prepare monographs on the evaluation of the carcinogenic risk of chemicals to man.

The following, taken from IARC Monograph Supplement 1 (1979) is of interest:

> "Selection of chemicals for evaluation is based on two criteria: firstly, there are data related to the carcinogenicity in humans or experimental animals; and secondly, there is evidence of human exposure.
>
> "Inclusion of a chemical in the monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic."

The fact that these monographs result from peer review of the existing data was the key factor in selecting the IARC list for the first annual report.

The approach for this first annual report is based on the IARC monograph program between 1971 and 1977 as summarized in the paper of Tomatis et al.: "Evaluation of the Carcinogenicity of Chemicals: A Review of the Monograph Program in the International Agency for Research on Cancer (1971 to 1977)," Cancer Research, 38: 877-885, April, 1978. This paper reported that "26 chemicals or industrial processes have been associated with, or are strongly suspected to be associated with, the occurrence of cancer in humans." These evaluations were "based on evidence provided by epidemiologic studies or case reports, and experimental evidence of carcinogenicity was not used in the formulation." These 26 chemicals or industrial processes associated with human cancer are the subject of the first annual report.

Subsequent to that article, the IARC Monograph Supplement 1, Chemicals and Industrial Processes Associated with Cancer in Humans, September, 1979, reviewed IARC Monographs, Volumes 1-20. The 1979 IARC Ad Hoc Working Group utilized case reports or epidemiological studies. Animal studies also were included in these evaluations as well as data that had become available since the publication of the relevant monograph.

The supplement established the following categories:

"Group 1: The chemical, group of chemicals, or industrial process is carcinogenic for humans. This category was used only when there was sufficient evidence to support a causal association between the exposure and cancer."

"Group 2: The chemical or group of chemicals is probably carcinogenic for humans."

"Group 2A: higher degrees of evidence"

"Group 2B: lower degrees of evidence"

"The data from experimental animal studies played an important role in assigning chemicals to category 2, and particularly to those in group B."

"Group 3: The chemical or group of chemicals cannot be classified as to its carcinogenicity for humans."

The list of the 26 IARC reviewed chemicals or industrial processes included in this report and their classification in Supplement 1 follows:

Substances	Monograph Volume and Page	IARC Supplement 1 Classification
1. aflatoxins	1, 145; 10, 51	2A
2. 4-aminobiphenyl	1, 74	1
3. arsenic and inorganic arsenic compounds	2, 48	1
4. asbestos	2, 17; 14 (entire volume)	1
5. auramine	1, 69	2B
6. benzene	7, 203	1
7. benzidine	1, 80	1
8. N,N-bis(2-chloroethyl)-2-naphthylamine	4, 119	1
9. bis(chloromethyl)ether	4, 231	1
10. cadmium and cadmium compounds	2, 74; 11, 39	2A
11. chloramphenicol	10, 85	3
12. chloromethyl methyl ether	4, 239	1
13. chromium	2, 100	1
14. cyclophosphamide	9, 135	2A
15. diethylstilbestrol	6, 55	1
16. hematite and iron oxide	1, 29	3
17. isopropyl oils	15, 223	3
18. melphalan	9, 167	1
19. mustard gas	9, 181	1
20. 2-naphthylamine	4, 97	1
21. nickel and nickel compounds	2, 126; 11, 75	1
22. oxymetholone	13, 131	2B
23. phenacetin	13, 141	2B
24. phenytoin and phenytoin sodium	13, 201	3
25. soots, tars, and oils	3, 22	1
26. vinyl chloride	7, 291; 19, 377	1

It should be noted that the IARC reports for each chemical include analyses of world-wide production, use and exposure (see Appendix). Since some of these data may not be appropriate to the United States, they have not been included in the report. The report is based on the participating agencies' submissions of

information relevant to Agency missions. The Agency positions in this area will be developed in the Appendix I: Agency Elaborative Statements on Regulatory Mission.

The summary of Agency submissions appears in Section F. Estimates of decrease of risk that participating Agencies were able to make as requested in the Act appear in Section E, under "Effect of Regulation and Other Actions."

Section E of this report includes a response to Section E of the Act requiring a description of information requests from a Federal Agency outside the DHHS or within DHHS to any other entity within DHHS to conduct research into, or testing for, the carcinogenicity of substances, and the responses made to such requests. Volume II contains IARC selected data, and the full Agency data submissions as received.

The second annual report will review (1) additional category 2A and 2B compounds; (2) selections from the IARC list of animal carcinogens; (3) those chemicals for which regulation has been completed and is based on the carcinogenicity of the chemical; and (4) those chemicals for which regulation has been formally initiated and is based on the carcinogenicity of the chemical.

C. Categories of Chemicals Catalogued

Tomatis et al., (Cancer Research 38: 877, April 1978), divided the chemicals or industrial processes evaluated in the first 16 of the IARC monographs into eight major use-exposure categories. In the following discussion, the 26 chemicals and industrial processses fall into five of these categories; namely, naturally occurring substances, industrial chemicals, industrial processes, industrial by-products and pharmaceuticals. Summary data relating to use and exposure, to evidence of carcinogenicity, and to kind and effectiveness of regulations in reducing exposure are provided.

1. Naturally Occurring Chemicals

The aflatoxins are the only chemicals on this list where exposure is principally from natural sources. Other chemicals on this list also exist in nature, to some degree, but their principal source of exposure is elsewhere. For example, soots are produced by fires in nature, as well as by those of human origin. Carcinogenic arsenic and metal compounds exist in rocks and soils and therefore may be present at low levels in food. For these, however, the highest level of exposure results from human activities. Therefore, these chemicals or industrial processes will be discussed in their appropriate category later in the report.

Aflatoxins

Aflatoxins are produced by some types of fungi that grow on food where high temperatures and high humidity favor their formation. Rapid post-harvest drying of crops and storage at low humidity are the most effective prevention and control measures. Grains, peanuts, tree nuts, and cotton seed meal or oil are among the more common substrates for the growth of these fungi. Meat, eggs, milk of livestock and other edible products from animals that consume aflatoxin-contaminated feeds may also contain aflatoxins.

Animal studies have shown that aflatoxins induce cancer in monkeys, marmosets, tree shrews, rats, mice, ducks and fish. Relatively high levels of aflatoxins have been found in the diet of human populations in Africa and Asia that have a high incidence of liver cancer. The 1979 IARC Ad Hoc Working Group which reviewed the IARC monographs classified the aflatoxins as probably carcinogenic for humans with "higher degrees of evidence."

Aflatoxin control is based on the authority of the FDA to limit the levels of environmental contaminants that are permitted in food. Complete elimination of aflatoxin contamination of food is neither technically nor economically feasible. Since only a small proportion of some foods are heavily contaminated while a larger proportion have very low levels of contamination, increasingly strict limits on aflatoxins in food would require elimination from the market place of an increasing proportion of these foods. The FDA has lowered the maximum amount allowed in food products as analytic methods of detection and methods of control have improved. An upper limit of 20 parts per billion (ppb) in shelled peanuts and peanut products and 0.5 ppb in milk is now in effect. A proposal, soon to be implemented, will lower the tolerance in peanut products to 15 ppb. The total amount of aflatoxins in the diet of Americans is estimated to be from 0.148 to 0.490 micrograms per person per day.

2. Industrial Chemicals

This category is composed of chemicals or mixtures of chemicals for which the major source of exposure results from industrial activity. The potential exposure hazard extends to uses, as well as to manufacture or production. It should be noted, however, that soots, tars, and oils are complex and variable mixtures, some of which may be carcinogenic and others not. The categories "Industrial Chemicals" and "Industrial Processes" (discussed subsequently) were those used by Tomatis et al. It is less clear for an industrial process which particular chemical is responsible for the carcinogenic hazard.

This category of industrial chemicals includes: 4-aminobiphenyl; arsenic; asbestos; auramine; benzene; benzidine; bis(chloromethyl) ether and chloromethyl methyl ether; mustard gas; 2-naphthylamine; soots, tars, and oils; and vinyl chloride. All of these, except auramine, were classified by the 1979 IARC Ad Hoc Working Group as being carcinogenic for humans. Auramine was classified as probably carcinogenic for humans with "lower degrees of evidence." The 1979 IARC Ad Hoc Working Group then noted that the manufacture of auramine is carcinogenic to humans.

4-Aminobiphenyl

This chemical, formerly used as a rubber antioxidant, has no commercial use in the United States today. It may be present, however, as a contaminant in diphenylamine which is used in the manufacture of dyes. As a result, there is an exposure potential to approximately 1,000 workers to 4-aminobiphenyl.

Carcinogenicity for the urinary bladder, liver, and other organs has been experimentally demonstrated in dogs, rats, mice, and rabbits. When it was used commercially, those workers exposed to 4-aminobiphenyl were found to have a high incidence of bladder cancer.

OSHA issued an emergency temporary standard in May 1973, followed by a final standard in February 1974, for control of worker exposure to diphenylamine by reducing exposure to the lowest feasible level. This was accomplished by prohibiting operations in open vessels, requiring use of exhaust fans, protective clothing, and respirators; and controlling plant contamination.

Arsenic

Production of arsenic and arsenical compounds in the United States is about 70 million pounds, while an additional 20 million pounds are imported. Occupational use of arsenic or materials contaminated with arsenic has the potential for exposing 545,000 workers, resulting from the manufacture or use of arsenic compounds in pesticides, glass, ceramics, paints, dyes, and preservation of hides. Arsenic is also present in the ores of a number of metals, resulting in potential exposure of workers and the environment from mining and smelting. In addition to occupational exposure, most of the population are exposed to low levels in food. Arsenic is found naturally in ocean fish and shellfish and trace residues may remain in tissues of livestock administered arsenical drugs and feed additives.

Evidence of the carcinogenicity of arsenic comes only from human studies. Skin cancer was found to be more common than usual among the following groups: patients receiving arsenic-containing drugs; inhabitants of areas with high levels of arsenic in the drinking water; and workers exposed to arsenic in several industries. There is also evidence suggesting that arsenic may be carcinogenic for the lung. Animal studies have not yet given convincing evidence of carcinogenicity. Additional experiments are in progress.

Levels in workplace air have been regulated since 1952. Current limits for inorganic arsenic, issued as a final standard by OSHA in June 1978, are 10 mg (μg) per cubic meter of air for eight hours. EPA limits arsenic in drinking water to a maximum of 0.05 mg per liter, and has proposed water quality criteria for total arsenic. Effluent guidelines control environmental release for certain industrial categories. EPA has issued a rebuttable presumption against the registration of eleven inorganic arsenical pesticides, a step in the possible banning or limiting of their use. FDA estimates that natural sources contribute 0.02 mg per day to the diet per person.

Asbestos

Asbestos is so widely used that our entire population is exposed to some level. Heavy exposure has occurred in the past to workers involved in the mining and milling of asbestos, the manufacture of asbestos-containing materials, application of asbestos insulation, and renovation of buildings and ships that used asbestos insulation. Families of workers have been exposed to asbestos-contaminated clothing that was brought home for cleaning. The domestic consumption of asbestos in 1976 was reported by the Bureau of Mines to be 726,300 short tons. About 2,500,000 workers have some occupational exposure during their work day. Exposure data relevant to consumer product uses of asbestos are now being collected by CPSC.

The general population is exposed to a large number of asbestos-containing products (listed in the CPSC portion of Volume II of this report) from which asbestos fibers may be released into the environment as a result of wear or deterioration. Asbestos that had been sprayed on interior surfaces of buildings as a fire retardant or decoration again may result in contaminating the inside air. The amount of asbestos to be found in food is assumed to be small, but confirmation is handicapped by lack of suitable monitoring techniques. Asbestos fibers have been found in the waters of rivers and lakes, particularly in asbestos mining areas.

Past occupational inhalation exposure to asbestos has been shown to increase the incidence of lung cancer. The effect is enhanced in those asbestos workers who also were cigarette smokers.

Asbestos exposure also causes mesotheliomas, malignant tumors of the lining of the chest or abdominal cavities. These ordinarily very rare tumors have been found at significantly higher rates in asbestos workers, also in their families, and are considered an asbestos specific disease. Cancer of the gastrointestinal tract and the larynx have also been shown to be increased in previously exposed workers. The carcinogenicity of asbestos for the lung and mesothelium has been confirmed by experiments in rats, mice, rabbits, and hamsters.

In 1976, OSHA reduced the concentration of asbestos fibers permitted in workplace air to two fibers per cc, the current standard. Primary reliance for control is based on engineering measures. The use of asbestos in clothing not designed for protection against thermal injury was banned by FDA in 1972. (Authority for ensuring compliance with this action has since been transferred to CPSC.) The banning by CPSC of asbestos in patching compounds and in gas fireplaces in 1977 prevented additional exposure of several million consumers who had already been exposed to asbestos from these sources. U.S. manufacturers of hand-held hair dryers cooperated with CPSC by voluntarily ceasing to use asbestos liners. This voluntary program resulted in the return to the manufacturer or the repair of 2 million of these dryers by January 1980. EPA proposed asbestos water quality criteria in October 1979. Air emissions are controlled through limits on visible emissions, labeling requirements and practice controls because of the lack of specific monitoring techiques for asbestos. A voluntary program launched by EPA with public schools is removing or encapsulating sources of asbestos release and exposure in school buildings. EPA and CPSC published advanced notices of proposed rulemaking stating their intent to further regulate the uses of asbestos.

Recently (April 1980) a NIOSH/OSHA work group reviewed the most recent scientific information and recommended that a new standard for asbestos be promulgated. Recommendations included reduction of the current environmental limit and elimination of non-essential asbestos exposures with substitution of less hazardous alternatives.

Auramine

Auramine is not manufactured in the United States, but about 500 pounds are imported annually. It is used industrially as a dye or dye intermediate for coloring textiles, paper and leather. About 3,000 workers in these industries may be exposed to auramine. Low-level dermal exposure may occur from use of these products by consumers.

Animal experiments, using commercial auramine of unknown purity, resulted in the induction of liver cancer in rats and mice. Workers engaged in the manufacture of auramine in open vessels had an increased incidence of bladder cancer. The workers, however, also were exposed to other chemicals. The 1979 IARC Ad Hoc Working Group classified auramine itself as probably carcinogenic for humans with "lower degrees of evidence."

The manufacture or use of auramine is subject to OSHA's general duty clause requiring that places of employment be "free from recognized hazards that are likely to cause death or serious harm" to employees.

Benzene

More than 16 billion pounds of benzene are produced each year in the United States and almost 3 billion pounds are imported. Nearly three million workers may be exposed, either through direct use of benzene or through the production and use of substances containing or contaminated with it. About 20 million people are estimated to be exposed to consumer products containing low levels of benzene as a contaminant. Benzene occurs in petroleum and coal-tar distillates. It has been used as a solvent in paints, adhesives, dyes, and in chemical laboratories. It is used in the manufacture of other chemicals, plastics, detergents, and certain pesticides. Benzene, alkanes, toluene, and xylene are added to most grades of gasoline. Benzene is most volatile of these aromatic hydrocarbons; this results in a benzene exposure not only to many thousands of gasoline filling station attendants, but to the innumerable motorists who are currently using self-service gasoline pumps. Depending upon the grade of gasoline and time of year, between one and four percent benzene is added to gasoline.

Reports of defects in blood cell formation and of leukemia among individuals who worked with benzene have appeared in medical literature since 1929. This evidence has been greatly strengthened by more recent epidemiological studies of benzene-exposed workers that support the conclusion that benzene causes leukemia in humans. While published animal experiments have not demonstrated carcinogenicity, those published so far have been inadequate. New studies are now underway in several laboratories.

OSHA's 1971 standard limited benzene to 10 ppm in the air for an eight hour time-weighted average (TWA). This was lowered in 1977 by an emergency temporary standard to a 1 ppm TWA with a maximum of 5 ppm for 15 minutes. A final standard establishing a permissible exposure limit of 1 ppm eight-hour TWA with a 5 ppm upper level limited to five minutes was stayed in court and is now under appeal. The Consumer Product Safety Commisson now requires warning labels on household products containing more than five

percent benzene. Safety packaging is required for solvents for paints or for other similar surface coating materials that contain at least ten percent benzene. In addition, the Commission has proposed a ban on the intentional use of benzene in consumer products and in products containing 0.1 percent or more of benzene by volume as a contaminant. Although a final regulation has not been issued, intentional use of benzene in consumer products has essentially been eliminated. Between 400,000 and 800,000 persons are no longer exposed as a result. EPA has proposed water quality standards for benzene and is working on air emission standards.

Benzidine

The use of benzidine, which was formerly produced in the United States at levels of many millions of pounds per year for the manufacture of dyestuffs, has fallen dramatically because of classic studies of carcinogenicity for humans and experimental animals. EPA figures indicate that only 500 pounds per year are now produced in the United States and none is imported. Production dropped substantially since EPA promulgated toxic pollutant effluent standards in 1977. Nevertheless, benzidine is used rather widely in small amounts in medical laboratories, and it is a contaminant in benzidine-based dyes. Accordingly, it is estimated that 86,000 workers may be exposed to some level of benzidine. In 1977, 1.4 million pounds of benzidine-based dyes were produced in the United States and 76,300 pounds were imported. "Benzidine-based" means that the chemical structure of benzidine is included as part of a larger molecule, even though the method of synthesis may not have required use of benzidine as a starting material. In addition to the problem of contamination of these dyes with free benzidine, there are recent data suggesting that some of the dyes may be metabolized inside the body, releasing free benzidine from the larger molecule.

Studies on occupationally exposed persons indicate that benzidine causes bladder cancer in humans. In experimental studies, it has induced liver and other cancers in rats, liver cancer in mice and bladder cancer in dogs.

EPA control activities for benzidine include both the 1977 toxic pollutant effluent standards and the water quality standards proposed in October 1979. CPSC reports that no insoluble benzidine-based pigments have been produced or imported into the United States since 1974, and that benzidine-based dyes are no longer being used in fabric dyes marketed for use by consumers. The Commission has received a petition requesting that benzidine-based dyes be banned for use in consumer products and is considering various regulatory alternatives. The OSHA standard, adopted in 1974, prohibits use of benzidine in open vessels and requires contamination control, use of exhaust fans, protective clothing and devices, and warning signs and labels.

Bis(chloromethyl)Ether and Chloromethyl Methyl Ether

These chemicals are the dichloro and monochloro derivatives of dimethyl ether. Technical grades of chloromethyl methyl ether (CMME) are contaminated with 1-8 percent bis(chloromethyl)ether (BCME). These chemicals are used in the synthesis of other chemicals and in the manufacture of plastics and ion exchange resins. Domestic production of BCME is reported by EPA to be 550,000 pounds. There are four producers of CMME in the U.S., but the amount produced has not been reported. No estimates of the number of workers exposed are available. Environmental exposure through water pollution should be small, since both chemicals rapidly break down in water. Breakdown in air would be less rapid, however. There is also the possibility of very low-level exposure to perhaps 100,000 dental patients per year from metabolism of some restorative materials. Significant concentrations of BCME are formed whenever formaldehyde, water and hydrogen chloride vapors are mixed at room temperature even in low concentrations. This potential route of exposure to BCME should not be overlooked for those situations where the potential for this reaction exists.

BCME has been studied in experiments in rats and mice. It produces tumors at the site of application, whether to the skin, subcutaneous tissues or respiratory tract. Technical grade CMME, which is contaminated with BCME, has also produced tumors in tests in mice but is less active than a similar amount of BCME. Epidemiologic studies have demonstrated an increased risk of lung cancer in workers exposed to BCME and technical grade CMME. The carcinogenicity of BCME is well established. There is debate, however, whether the carcinogenicity of CMME results from that chemical, from the contaminating BCME, or from their combination. Technical CMME, contaminated with BCME, is considered a potential human cancer hazard.

OSHA issued an emergency temporary standard covering both chemicals in 1973 and a final standard in 1974. This limits exposure to the lowest feasible level through prohibition of operation in open vessels and by the requirement for exhaust fans, control of contamination, protective clothing and devices, and warning signs and labels. EPA proposed general water quality criteria for chloroalkyl ethers in October 1979. These would include both BCME and CMME. The possible need for air emission regulations is being assessed.

Mustard Gas

Mustard gas was manufactured in the past for purposes of chemical warfare. It is not in the TSCA inventory of commercial chemicals, nor is any other information available indicating that

there is any manufacture, use or exposure in the United States at the present time.

The best evidence for carcinogenicity of mustard gas comes from a study of Japanese workers in a factory manufacturing this substance from 1929-45 where an increased incidence of cancer of the respiratory tract was observed. In experimental studies, it has increased the number of lung tumors in exposed mice.

Since there is no reported production or use, there are presently no specific regulations in effect for mustard gas. Should someone choose to make it, such manufacture would fall under OSHA's "general duty clause" requiring that places of employment be "free from recognized hazards that are likely to cause death or serious physical harm to his employees." In addition, under the Toxic Substances Control Act, it would be considered a new chemical and would have to meet the requirements of this Act.

2-Naphthylamine

Substantial amounts of 2-naphthylamine were made at one time for use in the dyestuffs industry. Since its carcinogenicity has become known, use has declined and has been discontinued in a number of countries. One American company reported 2-naphthylamine for TSCA inventory, but without indicating whether it manufactured or imported the chemical and without indicating the quantities involved. An estimated 1000 workers may be exposed, including some in research laboratories. 2-Napththylamine may be formed in small quantities from pyrolysis of nitrogen-containing organic matter. It is also a contaminant of 1-naphthylamine which has also been used in the dye industry.

Occupational exposure to 2-naphthylamine has been shown to cause bladder cancer in workers. It also induces bladder cancer in monkeys, dogs, and hamsters, and liver tumors in mice.

OSHA regulated worker exposure to 2-naphthylamine to the lowest feasible level through an emergency temporary standard in 1973 and a final standard in 1974. Operations in open vessels were prohibited and use of exhaust fans, contaminant controls, protective clothing and devices, and warning signs and labels are required.

Soots, Tars, and Oils

Each of these materials is a complex mixture derived from a number of different sources and composed of many ingredients. The nature of these ingredients depends on the source or method of

production of the material and on the extent to which the material is purified. "Oils" is a particularly broad term including many substances for which there is no evidence for carcinogenicity, in addition to the crude mineral oil lubricants and shale oil that have been shown to be carcinogenic. Thus, although materials known by each of these labels have been demonstrated to be carcinogehic, not all materials so named or all substances derived from these materials are carcinogenic. In each case, the carcinogenic chemicals within the mixtures constitute a small proportion of the total. They may be essentially all removed, for example, from carbon black which is derived from soot or from medicinal grade mineral oils purified from crude mineral oil. These facts should be kept in mind when considering levels of production or exposure cited in this report. On the other hand, combustion occurs widely in both industrial and non-industrial settings resulting in unintentional production of soot and volatile materials. Exposure figures from these sources are not included here, but it can be assumed that the entire population is exposed at some level. It is also apparent that total elimination of human exposure to carcinogenic products of combustion is not possible.

In 1975, domestic production of coal tar was reported to be almost 35 million pounds, while two million pounds of coal tar neutral oil were produced. One hundred twenty-one thousand workers were estimated to be exposed to tars. Production of creosote in the United States approached one billion pounds in 1976. Production figures relate to pesticides only.

Occupational exposure to the soot, tar, pitch and fumes from coal has caused cancer in humans at several sites. These materials contain carcinogenic chemicals classified as polycyclic aromatic hydrocarbons. Other chemical ingredients may also contribute to the carcinogenicity of these substances. Exposure to crude mineral oils and shale oil have also led to the development of cancer in humans. Animal experiments have demonstrated the carcinogenicity of coal-tars, soot, creosote oils, shale oils, and cutting oils. A number of polycyclic aromatic hydrocarbons extracted from some of these materials are carcinogenic in experimental animals.

OSHA established a permissable exposure limit for coal tar pitch volatiles of 0.2 mg per cubic meter as an eight-hour time-weighted average. EPA issued a rebuttal presumption against the registration of pesticides containing coal tar, coal tar neutral oil and creosote. Public responses to this are under review, and a determination is expected in 1980. FDA regulates the use of carbon black in food, drugs and cosmetics, use of petrolatum and mineral oil in food, and the use of coal tar in drugs. The use of carbon black as a coloring agent in food, drugs, and cosmetics has been prohibited since 1976. Carbon black may still be used in food packaging materials, but only if it is free of measurable polycyclic aromatic hydrocarbons and its migration into food is "nil." Petrolatum

and mineral oil may be used for coating fruits and vegetables and as a release agent for bakery products only if they do not contain polycyclic aromatic hydrocarbons. The use of coal tar for treatment of skin disorders is under review.

Vinyl Chloride

The principal use of vinyl chloride is in the production of plastics. It is also used in the synthesis of other chemicals and formerly was used as an aerosol propellant. Current annual domestic production is 6.9 billion pounds. More than 3.5 million workers are potentially exposed. In addition, 4.6 million people live within five miles of industrial sites at which environmental emissions could occur. Very low levels of exposure may occur from leaching into food or medical products from unreacted vinyl chloride remaining in polyvinyl chloride used for containers.

The first evidence of carcinogenicity in humans came from the observation of a rare type of cancer, angiosarcoma of the liver, in workers exposed to vinyl chloride. This has been confirmed in more extensive epidemiologic investigation. There is also evidence that the chemical causes tumors of the brain, lung, blood system, and possibly other organs in humans. Angiosarcoma of the liver, as well as other tumors, have been induced in mice, rats, and hamsters.

The occupational standard of 500 ppm, in effect since 1952, was lowered to 50 ppm by OSHA's emergency temporary standard of April 1974. A permanent standard of 1 ppm was proposed in May 1974, and adopted in October 1974. Medical surveillance, training for workers, use of protective clothing and respirators, warning signs and product labeling, a written compliance plan and periodic monitoring are required by OSHA. CPSC, FDA and EPA each banned the use of vinyl chloride as an aerosol propellant, eliminating exposure from the source of between one and five million people annually. EPA proposed water quality criteria in March 1979, and set the national emission standards for hazardous air pollutants, vinyl chloride, in 1976. FDA has also eliminated its use in drug products and has altered food manufacturers to the need to monitor packaging materials for vinyl chloride.

3. Industrial Processes

The industrial processes discussed here include: cadmium and cadmium compounds, chromium and chromium compounds, hematite and nickel and nickel compounds. All but cadmium and cadmium compounds and hematite were considered by the 1979 IARC Ad Hoc Working Group to be carcinogenic for humans. Cadmium and cadmium compounds were considered as probably carcinogenic for humans with "higher degrees

of evidence." Hematite could not be classified as to its carcinogenicity for humans. However, underground hematite mining was considered to be carcinogenic for humans. Although each process is identified by a particular chemical of interest in the process, that does not mean that the given chemical itself is carcinogenic in each of these processes. The actual chemical, or mixture of chemicals, responsible for human cancer in each case is unknown. In some processes, nickel or chromium for example, some of the named chemicals have been shown to be carcinogenic to experimental animals, but which specific nickel and chromium compounds in the process contributes to human risk of cancer is not known. While hematite itself has not been shown to be carcinogenic in experimental animals, underground hematite miners have an excess risk of lung cancer.

Cadmium and Cadmium Compounds

These chemicals are widely used commercially in electroplating, alloys, soldering, plastic stabilizers, batteries, fungicides, and in phosphors and pigments for television tubes, inks, artists' colors, glass, ceramics, textiles and paper. Cadmium is also present in zinc ores and may be released into the environment by smelters. Cadmum is found naturally at low levels in food and drinking water, but these levels may be increased by environmental contamination. Thus, the entire population is exposed to small amounts of cadmium in the diet (0.05-0.14 ppm) and drinking water and some unknown portion of the population through contact with cadmium-containing products. About 359,000 people have occupational exposure to cadmium and its compounds. Domestic production of cadmium and eight important compounds is 25 million pounds, while three million pounds are imported.

Several studies of occupational exposure to cadmium have suggested an increased risk of cancer of the prostate and possibly the respiratory tract. An IARC working group that evaluated the data in 1975 concluded that "occupational exposure to cadmium in some form. . . increases the risk of prostate cancer in man." The 1979 IARC Ad Hoc Working Group was more equivocal. They categorized the human evidence as "limited," a category between "sufficient" and "inadequate." "Limited evidence of carcinogenicity indicates a possible carcinogenic effect in humans, although the data are not sufficient to demonstrate a causal association." Several cadmium compounds have induced tumors at the injection site of rats. The significance of this as an indicator of carcinogenicity, in the absence of other types of evidence, is a subject of debate. Testicular tumors also have been induced in mice and rats, possibly because of effects on the pituitary gland. Thus, there are differences of opinion among scientists about the potential carcinogenicity of cadmium or its compounds for humans.

The maximum drinking water contamination by cadmium permitted by EPA is 0.01 mg per liter. This is under review. General water quality criteria were proposed in March 1979. EPA has issued a rebuttable presumption against registration of cadmium-containing pesticides, but final action has not been taken. OSHA standards set permissible exposure limits for cadmium fumes at 0.1 mg per cubic meter of air and for cadmium dust at 0.2 mg per cubic meter. Each of these is for an eight-hour time weighted average. FDA limits leaching from pottery and enamel to 0.5 mg.

Chromium and Chromium Compounds

Chromium in the form of chromium compounds is widely distributed in air, water, soil and food. It is an essential ingredient in our diet in trace amounts. The aggregate annual domestic production of chromium and ten important chromium compounds is over 900 million pounds. About 114 million pounds are imported. Chromium and its compounds are used in metal alloys such as stainless steel, as protective coatings on metal, on magnetic tapes, and as pigments for paints, cement, paper, rubber, composition floor covering, and other materials. The entire population is thus exposed to some of these substances, but levels of exposure obviously vary for different compounds. OSHA estimates that 4,400,000 people are exposed through their occupations.

Workers in the chromate-producing industry have an increased incidence of lung cancer. Chromium platers and chromium-alloy workers may also have an increased risk of lung cancer, bu the evidence is less conclusive. Animal experiments involving exposure to calcium chromate by several routes, including inhalation and intratracheal implantation, have demonstrated carcinogenicity. Several other chromate compounds, namely, strontium chromate, zinc chromate, and chromic chromate, produced local tumors at the site of injection. The animal data for other chromium compounds is inadequate. Thus it is clear that at least some chromium compounds are carcinogenic in animals and that chromium industry workers may have an increased risk of cancer. The particular compounds responsible for this risk are not clear.

OSHA's permissible exposure limits are 0.5 mg per cubic meter of air for soluble chromium compounds and 1 mg for chromium metal and insoluble compounds. The maximum level permitted in drinking water by EPA is 0.05 mg per liter. Water quality criteria were proposed in October 1979. Effluents are controlled through issuance of permits, including provisions of the applicable effluent guidelines at minimum.

Hematite

Hematite, a term for iron oxide or the ore from which it comes, is a major source of iron. Combined production and imports into this country, according to EPA figures, approach 2 billion pounds, making it one of the highest volume substances on this list. Present evidence, however, does not adequately demonstrate that hematite itself is carcinogenic to humans. Hematite miners working underground have been found to have an increased incidence of lung cancer. These miners also are exposed to silica dust, and exposure to the radioactive gas radon was found to occur in one hematite mine in England. Studies of surface miners and workers exposed to iron oxide from other occupations have not shown convincing evidence of carcinogenicity. Experiments exposing animals to ferric oxide have either been negative or inconclusive.

Regulation of conditions in mines falls under the Mine Safety and Health Administration. The "general duty clause" of OSHA would apply to general worker exposure.

Nickel and Nickel Compounds

Annual domestic production of nickel and 14 nickel compounds in 169 million pounds; 425 million pounds are imported. Major uses are in production of metal alloys, metal plating, batteries, spark plugs, ceramic glazes, pigments for paint, and catalysts used in the manufacture of organic chemicals, petroleum refining and hardening of edible oils. Estimates of workers exposed vary. Based on the National Occupational Hazard Survey data, OSHA estimates the number of workers exposed at 709,000. The entire population is exposed to low levels of nickel (300-600 micrograms per day) in food and water. Nickel compounds may become air pollutants from the combustion of coal, diesel oil and fuel oil.

Epidemiologic investigations of workers in several nickel refineries have shown an increase in cancer of the nasal cavity and of the lung. Other occupational groups exposed to nickel have not been adequately studied. Nickel subsulfide induced lung cancer in rats exposed by inhalation and produced injection site tumors in both rats and mice. Suggestive evidence of carcinogenicity by intravenous and inhalation routes of exposure in rats exists for nickel carbonyl, a possible air pollutant resulting from the burning of nickel-containing fuels. Other nickel compounds have not been adequately studied in animals by routes pertinent to human exposure. For example, nickel powder and several nickel compounds have produced tumors at the site of the injection; the significance of this route of exposure is unresolved. In summary, while nickel refinery workers have an increased risk of developing cancer, it is not known which one of the nickel compounds, or mixtures thereof, is carcinogenic.

The workplace exposure limit of 1 ppm for nickel carbonyl, in effect since 1952, was lowered by OSHA in 1971 to 0.001 ppm or 0.007 mg per cubic meter. For other forms of nickel, the permissible exposure limit is 1 mg per cubic meter as nickel and as metal soluble compounds. EPA established effluent guidelines for some industries and controls effluents by issuing permits. Water quality criteria were proposed in July 1979. The possible need for air quality regulation is being assessed.

4. Industrial By-Products

These are unintentional products of industrial activity. They are formed during the manufacture of some product of commercial use. Since they are not produced for their commercial value, they are often poorly characterized, and good production figures may be lacking. The only industrial by-products considered in this report are the isopropyl oils. These oils are formed during the manufacture of isopropyl alcohol. The 1979 IARC Ad Hoc Working Group stated that the isopropyl oils could not be classified as to its carcinogenicity for humans. Manufacture isopropyl of alcohol by the strong acid process was classified as carcinogenic for humans.

Isopropyl Oils

There are several industrial approaches for the manufacture of isopropyl alcohol. One involves the reaction of sulfuric acid with propylene gas. There are two processes using this approach: one uses stong sulfuric acid at moderate temperature; the other uses somewhat weaker acid at a higher temperature. In addition to producing isopropyl alcohol, these two processes leave a residue composed of a mixture of many organic chemicals. This residue is called isopropyl oils. Evidence of human carcinogenicity is limited to the strong acid process for the manufacture of isopropyl alcohol and the isopropyl oils associated with it. No figures are available on the quantity of isopropyl oils produced during the manufacture of isopropyl alcohol or worker exposure to them. Production figures for isopropyl alcohol are cited in this report; however, they are a poor indicator of worker exposure to the manufacture of isopropyl alcohol by the strong acid process, since newer processes have been replacing this one.

As increased incidence of cancer of the nasal sinuses and respiratory tract was found among workers in two factories that had produced isopropyl alcohol by the strong acid process. No studies of plants using other processes are available. Several experimental investigations of isopropyl oils produced by the strong acid process have suggested carcinogenicity but have not been definitive.

There are not any specific regulations regarding isopropyl oils. They would fall under OSHA's "general duty clause," however.

5. Pharmaceuticals

The heaviest exposure to pharmaceutical chemicals occurs among those patients being treated. Although of major concern to the Food and Drug Administration, these chemicals assume lower priorities for OSHA and EPA. In regulating pharmaceuticals, FDA is required to consider their benefits to health as well as their risks. Pharmaceutical chemicals are specifically excluded from the TSCA inventory of chemicals in commerce, though they may be listed in error or if they have other commercial usages. OSHA does not have specific regulations for workplace exposure to any of the pharmaceuticals listed here. Each, however, is covered by the requirement that places of employment be "free from recognized hazards that are likely to cause death or serious harm" to employees. All of the following pharmaceuticals as well as all human prescription drugs in oral dosage form (other than those specifically exempted) are subject to CPSC's Child Resistant Packaging Standards. These standards require packaging which will preclude entry by at best 80% of children under 5 years of age.

This category includes: N,N-bis(2-chloroethyl)-2-naphthylamine, chloramphenicol, cyclophosphamide, diethylstilbestrol (DES), melphalan, oxymetholone, phenacetin, and phenytoin. The 1979 IARC Ad Hoc Working Group classified diethylstilbestrol, melphalan, and N,N-bis(2-chloroethyl)-2-naphthylamine as carcinogenic for humans. Cyclophosphamide was classified by this Working Group as probably carcinogenic for humans with "higher degrees of evidence," while oxymetholone and phenacetin were classified as probably carcinogenic for humans with "lower degrees of evidence." This Working Group could not classify chloramphenicol and phenytoin with respect to their carcinogenicity for humans due to the inadequacy of the avalable data.

N,N-Bis(2-Chloroethyl)-2-Naphthylamine

This pharmaceutical chemical, also known as chlornaphazine, has been used in some countries to treat leukemia and related cancers. There is evidence that it has caused bladder cancer in humans, and it has caused tumors in experimental animals. It has not been produced or used commercially in the United States.

Chloramphenicol

This antibiotic is used and approved for treatment of bacterial and rickettsial infections in humans and non-food producing animals. Between 120,000 and 150,000 patients are treated each year. Although it is not approved for use in food-producing animals, some illegal use in animals results in some human exposure. FDA does not have a sufficiently sensitive monitoring technique to detect these possible residues for chloramphenicol in food.

The most important toxic effect of chloramphenicol therapy is damage to the bone marrow with reduction of blood cells. Estimates of the frequency of this effect range from one case in 24,500 to one case in 227,000 patients receiving chloramphenicol. Leukemia may develop in some patients who survive the bone marrow damage.

Chloramphenicol is regulated as a prescription pharmaceutical. Systemic dosage forms carry labels warning about carcinogenicity and advising that unnecessary exposure be avoided.

Cyclophosphamide

Cyclophosphamide is a prescription pharamceutical approved for treatment of cancer. It also has some investigational use for suppresing immunological activity in non-malignant diseases such as rheumatoid arthritis and the kidney diseases glomerulonephritis and the nephrotic syndrom. FDA estimates that 200,000-300,000 patients may be treated with it each year. Their daily dose is 15 mg per kilogram of body weight.

There has been a number of reported cancer cases arising some time after treatment of non-malignant disease and second cancers arising after treatment of an earlier cancer with cyclophosphamide. These were mostly leukemias and bladder cancer, but other types have been reported as well. An epidemiologic study of patients treated for cancer of the ovary with a number of different alkylating drugs, including cyclophosphamide, showed a subsequent increase in leukemias. These results suggest that this pharmaceutical can cause cancer in humans, but neither IARC working group regarded the evidence as definitive. Several studies in rats and mice have found cyclophosphamide to be carcinogenic.

Information warning of the danger of inducing cancer with this pharmaceutical is required in each package. Some of the non-malignant diseases for which this chemical may be used are extremely serious or fatal.

Diethylstilbestrol (DES)

This is a synthestic pharmaceutical developed to have the function of natural estrogens, hormones which are produced by the ovary. It is more effective after oral administration than natural estrogens. About 500,000 patients are treated each year with this pharmaceutical chemical, the majority for cancer of the prostate and other cancers. Other uses include treatment for menopausal and post-menopausal symptoms and breast engorgement following delivery. Most of the rest of the population was exposed to low levels (less than 10 ppb in the diet) because of its use as a growth promoter in cattle and sheep. This use is being reevaluated. During the 1940's

and 1950's, DES was prescribed extensively for the treatment of threatened miscarriage. This use declined following evidence that it was both ineffective and sometimes hazardous.

Several studies have found that a small proportion of the daughters of women exposed to relatively large doses of DES or other estrogens during pregnancy developed cancer of the vagina. This kind of cancer is ordinarily very rare. There is also evidence, though less conclusive, that prolonged treatment with DES can cause cancer of the uterus and breast. Experiments with several species, including monkeys, have shown that DES and other estrogens can cause cancer, especially in organs that are responsive to estrogens.

FDA's labeling requirements for DES include warnings to physicians and patients of the risk from treatment with estrogens. The labels specifically warn that DES should not be used during pregnancy. A regulation by FDA prohibiting the use of DES in food-producing animals has been challenged in court.

Melphalan

Melphalan is approved by FDA only for treatment of two types of cancer: multiple myeloma and cancer of the ovary. It also has some investgational use for other types of cancer. Between 30,000 and 50,000 patients may be treated each year.

There have been several case reports and two epidemiological studies showing that patients treated for one cancer with melphalan may develop another malignant tumor later. In most cases, the second cancer has been leukemia. several studies with rats and mice have demonstrated the carinogenicity of the drug.

Use is restricted to treatments approved by FDA.

Oxymetholone

Oxymetholone is a synthetic hormone having actions similar to those of the male hormone, testosterone. At one time, a major use was for treatment of anemias caused by deficient production of red blood cells. In 1972, however, FDA dropped its approval of this use since evidence supporting its effectiveness for this purpose was inadequate. Since then, the only approved use has been treatment of senile and post-menopausal osteoporosis, a condition in which bones become brittle. FDA's Bureau of Drugs estimates that 50-100,000 patients are treated each year with oxymetholone.

Several cases of liver tumors have been reported in patients treated for anemia for long periods with this and other androgenic pharmaceuticals (i.e., drugs having testosterone-like action). These pharmaceuticals may also cause severe damage to the liver, including the formation of blood cysts. Hemorrhage from these cysts can be a serious complication. There are no published studies of the possible carcinogenicity of oxymetholone in experimental animals. The evidence suggests that oxymetholone and other androgenic drugs may case liver tumors in humans, but neither of the IARC working groups that reviewed the data considered it to be conclusive.

As described above, FDA reduced the list of approved uses of oxymetholone in 1972. Since 1977, warnings of danger of liver damage and cancer have been required within the packages of this pharmaceutical.

Phenacetin

Phenacetin has been produced commercially in the United States for at least 50 years. It is generally mixed with other pharmaceutical agents and used in over-the-counter remedies for pain and fever. The widespread availability of these remedies indicates that a high proportion of the population may be exposed with doses ranging up to one gram per day. EPA figures indicate annual domestic production of 550,000 pounds, with 55,000 pounds being imported. The fact that some companies have reported phenacetin to the TSCA inventory of commercial chemicals suggests that phenacetin may have commercial uses other than as a pharmaceutical.

Several studies have reported that heavy, chronic use of pharmaceuticals containing phenacetin, by humans, may be associated with damage to the portion of the kidney where urine collects, and that cancer may develop in this region. Exposure was generally to mixtures of phenacetin with other pharmaceuticals. Although an eariler study in rats had been negative, an investigation published in 1979 reported an excess of urinary tract and nasal cancer in rats fed diets containig phenacetin. Liver tumors have also been induced in rats with N-hydroxyphenacetin. This chemical is though to be a possible metabolite of phenacetin. In 1979, the IARC Ad Hoc Working Group decided that there was "limited evidence" of carcinogenicity in humans and experimental animals.

After an advisory panel dtermined that phenacetin could not be considered "safe" for over-the-counter use, the FDA initiated administrative hearings to remove it from these products. This has been challenged by objections to the validity of the carcinogenicity data.

Phenytoin

Diphenylhydantoin, as this pharmaceutical is called in the United States, is one of the most important prescription pharmaceuticals for the control of epilepsy. Figures on the number of patients using it are not now available, but it is used by a major segment of the epileptic population.

Several case reports and epidemiological studies have found an increased incidence of malignant lymphomas in epileptics who were treated with this chemical. Some of them had also been treated with other pharmaceutical chemicals. One study reported a small increase in lymphomas in the children of epileptic mothers as well. One large epidemiological study of epileptics (over 9,000 cases) treated with phenytoin or other pharmaceutical chemicals failed, however, to find an excess of lymphomas. IARC working groups have noted the reported association between anti-convulsant therapy and lymphomas in humans, but the 1979 IARC Ad Hoc Working Group considered the evidence inadequate to allow a conclusion as to carcinogenicity for humans. Mice treated with phenytoin have developed an increase in lymphomas. Other species have not adequately tested.

The FDA has asked an advisory committee to assess the data and make a recommendation.

D. The Regulatory Council's Statement on Setting Priorities for Regulating Carcinogens and on Carcinogen Related Missions of NTP Participating Agencies

Each of the agencies participating in this effort have specific regulatory responsibilities with rspect to carcinogens assigned by law. These agencies coordinate their efforts in determining whether a chemical or industrial process may cause cancer, assessing the risk of cancer to humans, and setting priorities for regulating carcinogens. This coordination has been developed by the Interagency Regulaory Liaison Group (IRLG).

In October 1979, the Regulatory Council published in the Federal Register its "Statement on Regulation of Chemical Carcinogens, Policy and Request for Public Comment." This section of the report, taken from the Federal Register contains its statement on setting priorities for regulating carcinogens and brief summary statements for the Federal agencies paticipating in the National Toxicology Program.

SETTING PRIORITIES FOR REGULATING CARCINOGENS

"A substantial number of cancer-causing chemicals has already been identified. As other chemicals are tested, some of them also are likely to be found capable of producing cancer. In deciding which ones to regulate first, Federal agencies will generally assign higher priorities to substances for which:

- There is substantial evidence that the substance is likely to present a risk of human cancer. Epidemiological studies and/or animal testing are sources of such evidence.
- There is reason to believe that the level of human exposure and/or risk is high. Either quantitative or nonquantitative risk assessments may provide a basis for such belief.
- The exposed population is large or is of special concern, such as children.
- Regulatory action could significantly reduce the extent of intensity or human exposure.
- Regulatory action could reduce not only cancer risk but also other human health and environmental hazards.
- A substance is, or could be, available that would pose a lower risk of cancer or other serious human health problems, or available evidence otherwise suggests that the social and economic costs of regulation would be small.

The relative importance of these priority-setting criteria will necessarily vary from case to case, and in establishing their final priorities the agencies also consider:

- The requirements of applicable laws or court orders which may limit their flexibility to establish their own priorities.
- Their responsibilities for dealing with other health and environmental hazards.
- The regulatory actions being taken or planned by other agencies.

Although the agencies will continue to coordinate their regulatory actions, each agency will establish its own regulatory priorities. Specific substances usually are not equally important from the standpoint of every agency's statutory mission. As an example, one substance may provide a serious risk in consumer products, but present little risk to workers. The most effective public health protection would occur if the agency concerned with protecting workers gives the former a higher priority and the agency concerned with protecting consumers gives the latter a higher priority.

In general, the regulatory programs will provide the most public health protection if each agency dealing with a specific area of exposure places the highest priority on the substance which provides the greatest health risk in its area of concern. Otherwise, agencies might be regulating substances which are of relatively little importance in their area of concern, creating unnecessary regulations and costs, with little public health benefit, and putting off actions which would provide much more benefit. For these reasons, its is neither necessary nor desirable that all agencies assign the same priority to each substance."

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